SUMMARY OF BIOENGINEERING RESEARCH PARTNERSHIP GRANTS FOR THE OCTOBER 29, 1998, PROGRAM ANNOUNCEMENT

The following text provides a summary of grants for Bioengineering Research Partnerships (BRP's) sponsored by BECON member institutes and announced in the October 29, 1998, *NIH Guide* as PAS-99-010. The objective of the BRP is to support basic bioengineering research addressing important biological or medical problems with the work being done by a multidisciplinary research team which applies an integrative, systems approach to develop knowledge or methods to focus on the project objectives.

Grants funded from applications submitted in response to the BRP announcement are listed below in alphabetical order by the principal investigator's (PI's) last name. Other information provided for each grant includes PI affiliation, grant title, application number, funding organization, and a brief summary of the project.

1. Principal Investigator: Berns, Michael W.
Affiliation: University of California - Irvine
Title: Integrated Platform for Chemical Analysis of Live Cells
Application Number: RR14892-01
Funding Organization: National Center for Research Resources

Summary: The general objective of this project is to design, build, and test an integrated optical and microfluidics system that will enable the performance of novel biochemical assays in living cells. Specific project objectives are to (1) develop a laser microscope platform for single cell manipulation and analysis; (2) develop a multipurpose, modular microfluidics chip for single cell assay; and (3) develop a broad range of analytes which can be assayed in single cells. The device will be tested in biomedical systems relating primarily to cancer, and cell growth and development. However, it will have wide application to areas of molecular medicine, drug development, and biomedical research.

2. Principal Investigator: Chien, Shu
Affiliation: University of California - San Diego
Title: Molecular Basis of Endothelial Remodeling by Flow
Application Number: HL64382-01
Funding Organization: National Heart, Lung, and Blood Institute

Summary: The endothelial cells of the vasculature are constantly subjected to flow forces which vary with space and time. In the straight portion of the aorta, blood flow is primarily laminar and the shear stress is high. In the bends and branch points of the arteries, blood flow is unsteady and exhibits a disturbed flow pattern and flow separation, recirculation, and reattachment. These differential flow patterns are correlated with the preferential localization of atherosclerotic lesions. The goal of this project is to determine whether laminar flow and disturbed flow activate different molecular signaling pathways in the blood vessel wall to result in the expression of unique sets of genes that lead to the functional consequences of anti-atherosclerosis and pro-artherosclerosis, respectively. The proposal is based on partnerships among scientists with expertise in vascular biology, physiology, biomechanics, bioengineering, bioinformatics, cell biology, and molecular biology. Results from this study will generate new insights into the fundamental problem of mechano-chemical transduction and elucidate the molecular basis for the topographical nature of atherosclerosis. Also, the signaling molecules identified in this study could be potential therapeutic targets for modulating the balance between cell cycle arrest and proliferation.

3. Principal Investigator: Crandall, Edward D.
Affiliation: University of Southern California
Title: Absorption Mechanisms for Peptide/Protein Drugs via Lung

Application Number: HL64365-01
Funding Organization: National Heart, Lung, and Blood Institute

Summary: New biotechnology advances are leading to the production of numerous protein and peptide drugs that cannot achieve their therapeutic potential because of inefficient delivery. Recently, systemic drug delivery of therapeutic peptide and protein drugs via pulmonary routes has proven to be more effective than delivery via oral routes. However, information is lacking on specific pathways and transport processes in the lung alveolar epithelium. This represents the major barrier to drug absorption. The goals of this proposal are to understand the transport mechanisms and trafficking of peptides and proteins across the lung alveolar epithelium and to elucidate the properties contributing to differences in bioavailability of various compounds. Using experimental approaches which span cell biology to bioengineering, the results of this project should provide critical information on how to increase bioavailability and improve the strategies related to the design of peptide and protein drugs while at the same time retaining the integrity of necessary alveolar epithelial barrier properties.

4. Principal Investigator: Halperin, Henry R.
Affiliation: Johns Hopkins University
Title: Magnetic Resonance Guided Electrophysiology Intervention
Application Number: HL64795-01
Funding Organization: National Heart, Lung, and Blood Institute

Summary: A major limitation in studying arrhythmias in patients is the inability to accurately correlate anatomical and electrical information. Another major limitation is the inability to viaualize ablated areas of myocardium during catheter ablation procedures which makes it difficult to confirm the presence of ablated lesions in the desired locations. This project is aimed at developing imaging technologies that combine anatomic information with electrophysiologic testing and catheter ablation. Although these imaging technologies primarily will address atrial fibrillation, they should be broadly applicable to using MRI to guide interventional procedures in the heart and other organ systems.

5. **Principal Investigator: Hirschl, Ronald B.**
Affiliation: University of Michigan - Ann Arbor
Title: Total Liquid Ventilation: A Bioengineering Partnership
Application Number: HL64373-01
Funding Organization: National Heart, Lung, and Blood Institute

Summary: This project proposes studies to understand and optimize the technique of Total Liquid Ventilation (TLV) for treatment of patients with the Adult Respiratory Distress Syndrome (ARDS). ARDS is a devastating lung disease that affects 150,000 patients per year in the United States and has a mortality of greater than 40%. In TLV, the lungs are filled with a perfluorocarbon liquid and ventilated with a device that oxygenates and removes carbon dioxide from the perfluorocarbon. This proposal addresses several fundamental physiological and bioengineering issues that underlie progress toward establishing TLV as a clinical tool. Factors to be studied include control of filling and distribution of the fluorocarbon in the lung, parameters of gas transport by the liquid, and flow limitation during expiration. The proposal combines image studies, theoretical fluid dynamic analyses, and animal studies.

6. Principal Investigator: Hoffman, Eric A.
Affiliation: University of Iowa
Title: Image and Model Based Analysis of Lung Disease
Application Number: HL64368-01
Funding Organization: National Heart, Lung, and Blood Institute

Summary: With the emergence of innovative interventions in lung disease treatment at both early and

late stages, it has become clear that sensitive, objective, accurate, and repeatable measures must be developed to determine the presence and regional distribution of lung abnormalities. This proposal is aimed at bringing together a team of engineers, scientists, and physicians from six academic institutions to collaborate on developing the technologies which will allow the use of dynamic, volumetric X-ray CT to assess the lung. This effort will involve the development of a comprehensive model of the human lung based on measurements from non-invasive, dynamic, volumetric X-ray CT imaging that can be applied to the early and pre-clinical assessment of lung abnormalities.

7. Principal Investigator: Izatt, Joseph A.
Affiliation: Case Western Reserve University
Title: Partnership for Research in Optical Coherence Tomography
Application Number: EY13015-01
Funding Organization: National Eye Institute

Summary: This proposal represents a multidisciplinary approach to advance the state of the art in diagnostic anatomical and functional imaging *in situ* at the micron scale. This will be achieved by developing fundamental advances in the technology of Optical Coherence Tomography (OCT), validating new techniques using animal models, and employing new technologies in pilot clinical studies. The specific objectives of the proposal are to (1) enhance and expand the clinical utility of OCT by developing core technologies such as high frame imaging, ultrahigh resolution imaging, minimally invasive endoscopic and opthalmic delivery systems, and physiological function imaging; (2) apply these technologies for pilot studies of early cancer detection in the GI tract; (3) apply these technologies for studies of chemoprevention and early cancer detection in the lung; (4) improve the accuracy and safety of keratorefractive surgery; (5) improve imaging of retinal, subretinal, and vitreous pathologies; and (6) apply functional imaing technologies for the quantitative detection of retinal/choroidal blood flow and vitreoretinal strand motion in animals and humans.

8. Principal Investigator: Langer, Robert S.
Affiliation: Massachusetts Institute of Technology
Title: Microchip Drug Delivery System
Application Number: AI47739-01
Funding Organization: National Institute of Allergy and Infectious Diseases

Summary: The method by which a drug is delivered can have a significant effect on the drug's therapeutic efficacy. Controlled drug delivery can alleviate problems associated with conventional therapy by providing stable drug bioavailability in a therapeutically meaningful range and can be used to localize the therapy to the tissue site of interest. Recent studies have shown that it is possible to fabricate a solid-state silicon microchip in which a number of chemicals or drugs can be stored and released on demand by an external trigger. Based on this technology, it should be possible to fabricate a device that can be pre-programmed to deliver combination drugs in a pre-determined fashion. This novel delivery technology has broad utility in the biomedical areas of local delivery of anesthetics for pain management, sub-dermal delivery of vaccines, periodontal delivery of antibiotic and anti-inflammatory agents, localized delivery of anti-tumor and neoplastic agents, gene delivery, and delivery of antiarrhythmic agents. The objectives of this proposal are to (1) develop an active, silicon-based microchip for controlled release of drugs that con operate autonomously; (2) develop a passive, polymeric chip for the controlled release of drugs; (3) evaluate the biocompatibility of active and passive microchip delivery devices; and (4) evaluate the resulting drug release both *in vivo* and *in vitro*.

9. Principal Investigator: Ley, Klaus F.
Affiliation: University of Virginia
Title: Biomechanics of Leukocyte Adhesion Molecules
Application Number: HL64381-01
Funding Organization: National Heart, Lung, and Blood Institute

Summary: This proposal involves assembling a group of biomedical engineers and molecular biologists to focus on the biomechanics of adhesion molecules. Leukocyte and endothelial adhesion molecules govern the trafficking of cells in ischemia reperfusion, atherosclerosis, inflammation, immunity, cancer metastasis, and other processes. Some adhesion molecules, such as selectins, are specialized to mediate adhesion in the presence of blood flow. Quantitative measurements of forces and displacements generated by adhesion molecules at the molecular level and quantitative measurements at the cellular level when the adhesion molecules are clearly identified have not previously been feasible. This group of investigators proposes to lead the way in the emerging field of adhesion molecular biomechanics by providing an understanding of detailed molecular biomechanics of selectins and their ligands. This objective is critical to understanding many areas of vascular biology and pathology such as atherosclerosis and thrombosis. Advances in this area will also provide the basis for the construction of new diagnostic and therapeutic vehicles to detect and treat disease processes associated with inflammation and will impact drug and gene delivery in the vascular system.

10. Principal Investigator: Olsen, Donald B.
Affiliation: Utah Artificial Heart Institute
Title: Magnetically Suspended Rotor Blood Pump
Application Number: HL64378-01
Funding Organization: National Heart, Lung, and Blood Institute

Summary: The objective of this proposal is to develop a novel ventricular assist device for patients suffering from congestive heart failure. Several new technologies will be developed to overcome shortcomings of existing blood pump technology. Most important will be the development of a totally magnetically suspended impeller to eliminate the need for contact bearings and seals. Additionally, a responsive physiologic controller will be developed to match system output to patient need without the use of sensors. These technological developments will benefit CHF patients by providing devices with significantly improved system reliability and durability, quality of life, and reduced anticoagulation needs. The proposed completely implantable, continuous flow, ventricular assist device will initially be intended as a bridge to transplantation, but the reliability characteristics should ultimately facilitate development of a longer term bridge to recovery or a permanent device.

11. Principal Investigator: Rylander, H. Grady
Affiliation: University of Texas at Austin
Title: Polarization Sensitive Retinal Tomography for Glaucoma
Application Number: EY12877-01
Funding Organization: National Eye Institute

Summary: This proposal is based on the hypothesis that the retinal nerve fiber layer displays a characteristic descrease with the development and progression of glaucoma. The project is aimed at developing a diagnostic modality based on the polarization and coherent properties of light for morphologic and functional imaging of the eye. Measuring depth-resolved polarization changes of light reflected from the retina will allow determination of both retinal nerve fiber layer thickness and axon density.

12. Principal Investigator: Sklar, Larry A.
Affiliation: University of New Mexico
Title: 7TMR Drug Discovery, Microfluidics, and HT Flow Cytometry
Application Number: GM60799-01
Funding Organization: National Institute of General Medical Sciences

Summary: High throughput (HT) screening is integral to drug discovery. While flow cytometry is known for its ability to measure cell responses, its power in the homogeneous analysis of ligand binding or molecular assembly and its potential for high throughput are not well recognized. This proposal consists of four projects targeted at displaying virtually any molecule in a format compatible with particle-based analysis and developing a novel approach for plug-flow cytometry with sampling times of about one second which would make flow cytometry a powerful alternative for the real-time analysis of molecular interactions. The four projects include (1) expressing the proteins relevant to to signal transduction and termination in forms appropriate for flow cytometry, (2) employing biomaterial display and detection strategies compatible with flow cytometric analysis, (3) developing applicable fluid handling approaches for cells and beads, and (4) developing and implementing micro-fluidic sample handling approaches using novel elastomer-based micromachine technology. The expected test platforms for high throughput analysis to be developed during this project will have commercial potential in drug development and will allow definition of mechanistic details of cell activation through 7TMR mediated pathways.

13. Principal Investigator: Westenskow, Dwayne R.
Affiliation: University of Utah
Title: Data Display to Detect-diagnose-Treat Critical Events
Application Number: HL64590-01
Funding Organization: National Heart, Lung, and Blood Institute

Summary: This project seeks to enhance a clinician's ability to discover and rapidly respond to critical events by developing displays that help to visualize the patient's physiologic state. The hypothesis is that object-oriented graphical displays that map closely the physician's mental models of the actual physiological processes will facilitate faster recognition of abnormal states, reduce errors, and shorten treatment time. The display is to provide a comprehensive view of the surgical patient's physiologic state. The proposed research will identify the type of display which optimally informs the anesthesiologist to rapidly detect physiologic changes, to make accurate diagnostic decisions, and to efficiently treat critical events. The final display should enhance patient safety during anesthesia and reduce morbidity.

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